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UTILITY PATENT APPLICATION TRANSMITTAL

for new nonprovisional applications under 37 C.F.R. § 1.53(b)

Attorney Docket No.

PC10139A MAG

First Named Inventor or Application Identifier

Nancy J. Harper

Title

Sertraline Oral Concentrates

Express Mail Label No.

EJ248206049US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO:

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Box Patent Application
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1. ☒ *Fee Transmittal Form (e.g., PTO/SB/17)
(Submit an original, and a duplicate for fee processing)
2. ☒ Specification [Total Pages 19]
(preferred arrangement set forth below)
- Descriptive title of the Invention
 - Cross References to Related Applications
 - Statement Regarding Fed sponsored R&D
 - Reference in Microfiche Appendix
 - Background of the Invention
 - Brief Summary of the Invention
 - Brief Description of the Drawings (if filed)
 - Detailed Description
 - Claim(s)
 - Abstract of the Disclosure
3. ☐ Drawing(s) (35 U.S.C. 11.3) [Total sheets]
4. ☒ Oath or Declaration [Total pages 2]
- a. ☒ Newly executed (original)
- b. ☐ Copy from a prior application (37 CFR § 1.63(d))
(for continuation/divisional with Box 17 completed)
[Note Box 5 below]
- i. ☐ **DELETION OF INVENTOR(S)**
Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).
5. ☐ Incorporation By Reference (useable if Box 4b is checked)
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6. ☐ Microfiche Computer Program (Appendix)
7. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
- a. ☐ Computer Readable Copy
- b. ☐ Paper Copy (identical to computer copy)
- c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. ☒ Assignment Papers (cover sheet & document(s))
9. ☐ 37 C.F.R. § 3.73(b) Statement ☐ Power of Attorney
(when there is an assignee)
10. ☐ English Translation Document (if applicable)
11. ☒ Information Disclosure Statement (IDS)/PTO-1449 ☒ Copies of IDS Citations
12. ☒ Preliminary Amendment
13. ☒ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
14. ☐ *Small Entity ☐ Statement filed in prior application, Status still proper and desired
(PTO/SB/09-12)
15. ☐ Certified Copy of Priority Document(s)
(if foreign priority is claimed)
14. ☐ Other:

*NOTE FOR ITEMS 1 & 14: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

17. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in a preliminary amendment:

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No: ____ / ____

Prior application information: Examiner _____ Group/Art Unit: _____

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: Examiner:To Be Assigned

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: Art Unit: To Be Assigned

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PRELIMINARY AMENDMENT

FOLLOWS:

in the specification.

Immediately following the title:

Application No. 60/104,024 filed October 13, 1998.--

A Notice of Allowance is courteously solicited.

Respectfully submitted,

Date: 10/11/99

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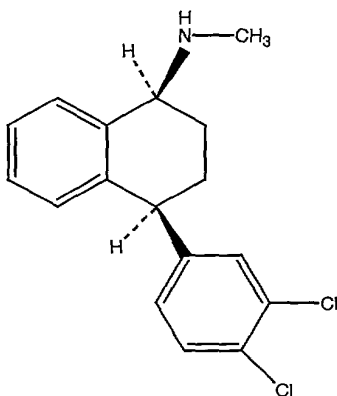
SERTRALINE ORAL CONCENTRATE

FIELD OF THE INVENTION

The present invention provides an essentially nonaqueous, liquid
5 pharmaceutical concentrate composition for oral administration containing sertraline
or a pharmaceutically acceptable salt thereof and one or more pharmaceutically
acceptable excipients. The present invention also provides a use of this concentrate
composition to prepare an aqueous solution of sertraline. In addition, the present
invention provides a method of using this concentrate composition to treat or prevent
10 a variety of diseases or conditions. Finally, the present invention provides the
compound, (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-
naphthalenamine methanesulfonate.

BACKGROUND OF THE INVENTION

15 Sertraline is a known compound having the following structure:



Sertraline has the following chemical name: (1S-cis)-4-(3,4-dichlorophenyl)-
20 1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine. Sertraline and its pharmaceutically
acceptable acid addition salts, such as the hydrochloride salt, are disclosed in U.S.
Patent No. 4,536,518, which issued on 20 August 1985, (hereafter referred to as the
'518 patent), which is herein incorporated by reference in its entirety. Another
pharmaceutically acceptable salt of sertraline is the mesylate salt.

25 The '518 patent states that sertraline and derivatives thereof are useful as
antidepressant agents. U.S. Patent No. 5,130,338, which issued on 14 July 1992,
refers to the use of sertraline to treat chemical dependencies, including dependencies

on alcohol, tobacco and cocaine. U.S. Patent No. 4,962,128, which issued on 9 October 1990, refers to the use of sertraline to treat anxiety related disorders such as panic disorder, obsessive-compulsive disorder, generalized anxiety disorder, phobias, post traumatic stress disorder and avoidant personality disorder. U.S. Patent No. 4,940,731, which issued on 10 July 1990, refers to the use of sertraline to treat premature ejaculation. Published PCT patent application, WO 96/22085, which was published on 25 July 1996, refers to the use of sertraline to treat cancer patients. Published European patent application 0768083, which published on 16 April 1997, refers to the use of sertraline to treat post myocardial infarction patients.

U.S. Patent No. 5,597,826, which issued on 28 January 1997, relates to novel compositions containing a serotonin selective reuptake inhibitor (SSRI), such as sertraline, and an agonist or antagonist of the serotonin 1 (5-HT₁) receptor and to the use of such compositions for treating or preventing a condition selected from mood disorders, including depression, seasonal affective disorders and dysthymia, anxiety disorders, including generalized anxiety disorder and panic disorder; agoraphobia, avoidant personality disorder; social phobia; obsessive compulsive disorder; post-traumatic stress disorder; memory disorders including dementia, amnesic disorders and age-associated memory impairment; disorders of eating behavior, including anorexia nervosa and bulimia nervosa; obesity; cluster headache; migraine; pain; Alzheimer's disease; chronic paroxysmal hemicrania; headache associated with vascular disorders; Parkinson's disease, including dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias; endocrine disorders such as hyperprolactinaemia; vasospasm (particularly in the cerebral vasculature); hypertension; disorders in the gastrointestinal tract where changes in motility and secretion are involved; sexual dysfunction, including premature ejaculation; and chemical dependencies. The foregoing published applications and U.S. patents are herein incorporated by reference in their entireties.

As noted above, sertraline hydrochloride is a selective serotonin reuptake inhibitor (SSRI) for oral administration. (Physicians' Desk Reference (PDR), 52nd ed., Supplement A, pages A250-A255 (1998).) Its mechanism, pharmacokinetics, and metabolism confer safety, once-daily dosage and efficacy in the treatment of depression, obsessive-compulsive disorder and panic disorder. It is approved for the treatment of one or more of these indications in over 60 countries worldwide. The daily doses for sertraline, expressed as the free base, range from 50-200 mg,

increasing in 50 mg increments. A titration dose of 25 mg/day during the initial phase of therapy may be warranted in some indications.

Tablet and capsule formulations of sertraline hydrochloride are commercially available in different countries. Capsular-shaped, scored tablets are available in strengths of 50 and 100 mg and are sold under the brand name, ZOLOFT® Tablets, in the U.S. The capsules are available in some countries in strengths of 50 mg and 100 mg.

The '518 patent discloses that sertraline and related compounds can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically-acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, aqueous suspension, injectable solutions, elixirs, syrups, and the like. According to this patent, when aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening, or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

However, development of an oral liquid dosage form of sertraline has been complicated by the objectionable bitter taste and astringency sensation imparted by the drug in liquid form. Thus, direct ("ready-to-use") oral liquid solutions or suspensions of sertraline, such as those described in the '518 patent above, have an objectionable taste, despite the inclusion of a variety of taste-masking or flavoring agents.

An oral liquid dosage form of sertraline with acceptable taste would be a valuable addition to the existing formulations, providing greater choice for both the prescriber and the patient. This is of importance with regard to the issue of non-compliance with treatment, which is believed to affect up to 50% of outpatients and appears to be a particular problem with elderly, pediatric and psychiatric patients (B. Blackwell, Drug Therapy: Patient Compliance, N.Engl.J.Med. 1973, 289(5):249-52). By virtue of being easier to swallow, an oral liquid dosage form of sertraline would offer an alternative to those patients who dislike or have difficulty swallowing tablets or capsules, and would therefore be of considerable benefit in treating those who may be non-compliant for those reasons. Therefore, there is a need in the art

for an alternative liquid dosage form of sertraline that has acceptable taste and properties.

Oral concentrate drug products are known in the art and are commercially available. However, these concentrates are conventionally aqueous. For example, NAVANE® Concentrate contains the active ingredient, thiothixene hydrochloride, and the inert ingredients of alcohol, cherry flavor, dextrose, passion fruit flavor, sorbitol solution and water. (Physicians' Desk Reference (PDR), 52nd ed., pages 2192-2193 (1998).) SINEQUAN® Concentrate contains the active ingredient, doxepin hydrochloride, and the inert ingredients of glycerin, methylparaben, peppermint oil, propylparaben and water. (Physicians' Desk Reference (PDR), 52nd ed., pages 2203-2204 (1998).) TRILAFON® Concentrate contains the active ingredient, perphenazine, and the inert ingredients of alcohol, citric acid, flavors, menthol, sodium phosphate, sorbitol, sugar and water. (Physicians' Desk Reference (PDR), 52nd ed., pages 2666-2668 (1998)).

SUMMARY OF THE INVENTION

The present invention particularly provides:

A pharmaceutical composition which comprises:

an essentially nonaqueous, liquid concentrate for oral administration

comprising an amount of sertraline or a pharmaceutically acceptable salt thereof and one or more essentially nonaqueous pharmaceutically acceptable excipients; wherein at least one of the excipients is liquid. Preferably, the pharmaceutically acceptable salts of sertraline are the hydrochloride salt and the mesylate salt.

More particularly, the present invention provides this composition wherein the concentrate contains sertraline hydrochloride, ethanol and glycerin. More specifically, in this concentrate, the sertraline hydrochloride is present in an amount of about 15 to about 30 mg/ml and the ethanol and glycerin are present at about 8 to about 20% ethanol (by weight) in glycerin.

The present invention also provides this composition wherein the concentrate contains sertraline hydrochloride, ethanol, glycerin and menthol. More specifically, in this concentrate, the sertraline hydrochloride is present in an amount of about 15 to about 30 mg/ml, the ethanol and glycerin are present at about 8 to about 20% ethanol (by weight) in glycerin, and the menthol is present in an amount of about 0.01 to about 5.0 mg/ml.

Most particularly, the present invention provides this composition wherein the concentrate contains sertraline hydrochloride, glycerin, ethanol, butylhydroxytoluene (BHT) and menthol. More specifically, each ml of this concentrate contains about 22.4 mg of sertraline hydrochloride, about 151 mg of ethanol, about 0.50 mg of menthol, about 0.10 mg of BHT, and a sufficient quantity of glycerin (which is about 1011 mg) to produce about 1 ml .

The present invention also provides the use of this essentially nonaqueous, liquid concentrate of sertraline or a pharmaceutically acceptable salt thereof to prepare an aqueous solution of sertraline which comprises: diluting the concentrate in an aqueous diluent prior to oral administration. Preferably, the pharmaceutically acceptable salts of sertraline are the hydrochloride salt and the mesylate salt.

The present invention also provides a method of treating or preventing diseases or conditions which are caused by disorders of the serotonergic system which comprises: a) diluting this concentrate in an aqueous diluent; and b) orally administering the resulting aqueous solution to a patient in need thereof. In addition, the present invention provides this method for treating or preventing diseases or conditions, such as the following: depression, anorexia, chemical dependencies, anxiety-related disorders (such as panic disorder, obsessive-compulsive disorder, generalized anxiety disorder, phobias, post traumatic stress disorder and avoidant personality disorder), premature ejaculation, cancer and post myocardial infarction.

The present invention also provides a process for making this essentially nonaqueous, liquid concentrate of sertraline or a pharmaceutically acceptable salt thereof.

Finally, the present invention provides the compound, (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine methanesulfonate.

DETAILED DESCRIPTION OF THE INVENTION

"Essentially nonaqueous" when used herein refers to the amount of water that is present in the final drug product, which amount is consistent with the amount of water potentially contributed by the active ingredient and/or by the excipients; however, no water is directly added to the final drug product. About 10% is the upper limit of the amount of water that may be present in the oral concentrate of the present invention. Typically, the amount of water that is present in the oral concentrate of the present invention ranges from about 0.8% to about 5.2% of the composition. Most

typically, the amount of water that is present ranges from about 0.8% to about 2.0% of the composition.

“Concentrate” when used herein refers to a strong solution provided for dilution before use. (Butterworths Medical Dictionary, 2nd edition, Butterworths, London - Boston 1978, pp. 399-400.)

“Pharmaceutically acceptable excipient,” as used herein, means a pharmacologically inactive ingredient which is used to formulate a drug product and which is readily known and available in the pharmaceutical arts. Examples of such excipients are given below.

“Pharmaceutically acceptable preservative,” as used herein, means an additive or excipient that preserves the quality of the formulation from a chemical or microbiological standpoint. Examples of preservatives are given below.

“Serotonergic system” when used herein refers to the neuronal process whereby serotonin is released by a pre-synaptic cell upon excitation and crosses the synapse to stimulate or inhibit the post-synaptic cell.

“Therapeutically effective amount,” as used herein, means an amount of a compound, e.g., sertraline or a pharmaceutically acceptable salt thereof, that ameliorates, attenuates, or eliminates one or more symptoms of a particular disease or condition or prevents or delays the onset of one or more symptoms of a particular disease or condition.

The sertraline oral concentrate of the present invention is a new dosage form of sertraline intended as a multidose product for oral use only. The oral concentrate is an essentially non-aqueous, optionally flavored solution of sertraline, preferably as the hydrochloride salt, which is intended to be diluted prior to administration.

The oral concentrate of the present invention is advantageous because, *inter alia*, it provides convenience in measuring different doses, which are needed for certain indications, and acceptable taste upon administration, as well as good physical/chemical stability characteristics throughout the product's shelf-life and use interval. Also, since the concentrate of the present invention is a solution, it is preferred over a suspension for ease of manufacture and optimal control of dosing homogeneity.

The active ingredient in the concentrate of the present invention is sertraline, which may be present as its free base or as its pharmaceutically acceptable salt. Such salts include, for example, the hydrochloride salt and the methanesulfonate salt

(also known as the mesylate salt). In the concentrate of the present invention, the hydrochloride salt is preferred.

5 The preparation of sertraline and its hydrochloride salt is described in the '518 patent referenced above, particularly in Example 2 of that patent. The mesylate salt is prepared by reacting the sertraline free base with methanesulfonic acid at room temperature in a solvent, such as ethyl acetate, methanol, ethanol and isopropanol. The mesylate salt has favorable properties, such as solubility in polar vehicles and good chemical stability.

10 Sertraline hydrochloride may be present in the concentrate of the present invention in an amount of about 1 mg/ml up to about 88 mg/ml of the composition. Preferably, it is present in an amount of about 15 to about 30 mg/ml of the composition. Most preferably, about 20 mg sertraline per ml, which is equivalent to about 22.4 mg/ml as the hydrochloride (assuming a theoretical stoichiometric potency of 89.4%), is present. The quantity of sertraline hydrochloride needed to produce a
15 concentration of about 20 mg sertraline per ml is adjusted based on the actual potency of the drug substance lot to be used.

One or more pharmaceutically acceptable excipients are present in the concentrate of the present invention. Examples of such excipients include the following: ethanol, glycerin (also referred to as glycerol or glycerine), propylene glycol
20 and polyethylene glycols. All of these excipients are well known in the pharmaceutical arts and are commercially available.

From among these excipients, binary combinations of ethanol and glycerin provide maximum solubilization of the sertraline hydrochloride drug substance and are preferred. In these combinations, the amount of ethanol that is present is about
25 8% to about 50% (w/w) in glycerin; preferably, about 8 to about 20% (w/w) ethanol in glycerin is present; most preferably, about 10 to about 14% (w/w) ethanol in glycerin is present. The ethanol that may be used in the concentrate of the present invention is any compendial grade of ethanol, including ethanol (95%) and anhydrous ethanol.

30 The concentrate of the present invention optionally contains one or more flavoring agents or taste-masking flavors. Examples of candy-type flavoring agents include mint, citrus and fruit flavoring agents. The mint flavoring agents, such as peppermint, spearmint and menthol (also referred to as levomenthol), are preferred. More specifically, from among a variety of mint flavoring agents, menthol is preferred and may be present in an amount of about 0.01 to about 5.0 mg/ml of the

composition; preferably, menthol is present in an amount of about 0.5 mg/ml of the composition.

The concentrate of the present invention also optionally contains one or more pharmaceutically acceptable preservatives, which preserve the quality of the concentrate from a chemical or microbiological standpoint. Preservatives, such as antioxidants, metal chelators, metal complexing agents and antimicrobial agents, may be used in the concentrate of the present invention. These preservatives may be used in the concentrate, both alone and in various combinations (e.g., antioxidant(s) in combination with a metal complexing agent), to improve product stability. When the concentrate of the present invention contains ethanol, it may be appropriately microbiologically self-preserved.

Examples of preservatives, which may be present in the concentrate of the present invention, include the following: butylhydroxytoluene (BHT, also referred to as butylated hydroxytoluene), butylated hydroxyanisole (BHA), propyl gallate, ascorbic acid, ascorbyl palmitate, sodium metabisulfite, sodium bisulfite, sodium thiosulfate, sodium hydroxide, cysteine, ethylenediamine tetraacetic acid (EDTA) or its salts (such as the sodium salt), citric acid, triethanolamine, thioglycerol, methylparaben and propylparaben. Also, various combinations of these preservatives may be present in the concentrate of the present invention, such as the following: disodium EDTA and BHA; disodium EDTA, BHA and BHT; disodium EDTA and propyl gallate; and BHA and BHT.

The amount of preservative that may be present in the concentrate of the present invention ranges from about 0.01 to about 10.0 mg/ml of the composition. In the concentrate of the present invention, butylhydroxytoluene (BHT) is preferred and may be present in an amount of about 0.01 to about 0.5 mg/ml of the composition; preferably, it is present in an amount of about 0.01 to about 0.2 mg/ml of the composition; more preferably, it is present in amount of about 0.01 to about 0.13 mg/ml of the composition; most preferably, it is present in an amount of about 0.05 to about 0.11 mg/ml of the composition.

The sertraline oral concentrate of the present invention is intended to be diluted in a suitable diluent or beverage prior to administration. For example, doses of the oral concentrate (equivalent to from about 25 mg to about 200 mg of sertraline) are mixed with approximately 4 oz. (about 120 ml or 1/2 cup) of a suitable diluent or beverage. The following beverages may be used for the preparation and

administration of the dose: water, orange juice, ginger ale, lemon-lime soda, lemonade, sugared tap water, cranberry juice, grapefruit juice, tomato juice, pineapple juice, prune juice, orange drink and Gatorade® (beverage, not powder). Water, orange juice, ginger ale, lemon-lime soda and lemonade are preferred. The proper dose of sertraline oral concentrate may be most conveniently added to these beverages by means of a dropper calibrated at, for example, 25 and 50 mg (as sertraline).

The manufacture of sertraline oral concentrate utilizes conventional pharmaceutical equipment and processes. For example, the manufacturing process for sertraline hydrochloride oral concentrate involves dissolving the sertraline hydrochloride drug substance in a solution of glycerin, ethanol, and optionally other excipients, such as butylhydroxytoluene (BHT) and menthol, followed by clarifying filtration, if desired, and filling into containers such as bottles, as appropriate.

Preferably, to facilitate BHT incorporation, this component is first dissolved in a portion of the ethanol, which is then added to the main compounding tank containing the glycerin and the remainder of the ethanol. Menthol and sertraline hydrochloride are then sequentially added and mixed to dissolve. The sertraline hydrochloride is intentionally added to the solution last to optimize the protective effect of the antioxidant (BHT). The compounded solution is passed through a filter, and the final product is filled into appropriate containers, such as bottles. The final product may be supplied in a variety of presentations, such as a 60 ml presentation, which is packaged in, for example, a 60 ml, amber glass bottle with a child-resistant closure.

CONFIDENTIAL

EXAMPLES

EXAMPLE 1

Concentrate solution (20 mg sertraline/ml) with preservative and menthol flavoring:

5

Ingredients	mg/ml	% w/v (g/100ml)	mg/60ml
Sertraline HCl	22.37	2.237	1342.3
Ethanol (95%)	150.68	15.068	9040.8
Menthol	0.50	0.050	30.0
BHT	0.10	0.010	6.0
Glycerin	1010.81	101.081	60648.6
Total	1184.46	118.446	71067.7

- 10 BHT, menthol and drug were dissolved in a mixture of glycerin and ethanol. The resulting mixture may be blanketed with nitrogen due to the ethanol content and associated potential flammability. The resulting mixture may be filtered, if desired.

EXAMPLE 2

One ml of a nonaqueous solution containing 1-23 mg sertraline HCl/ml:

Sertraline Hydrochloride: 1 - 23 mg

Polyethylene glycol 300 (PEG-300): sufficient quantity to produce 1 ml

- 15 Dissolve the drug substance in the PEG with stirring.

EXAMPLE 3

One ml of a nonaqueous solution containing 1 - 64 mg sertraline HCl/ml:

Sertraline Hydrochloride: 1 - 64 mg

Propylene Glycol: sufficient quantity to produce 1 ml

- 20 Dissolve the drug substance in the propylene glycol with stirring.

EXAMPLE 4

One ml of a nonaqueous solution containing 1 - 17 mg sertraline HCl/ml:

Sertraline Hydrochloride: 1 - 17 mg

Ethanol: sufficient quantity to produce 1 ml

- 25 Dissolve the drug substance in the ethanol with stirring.

EXAMPLE 5

One ml of a nonaqueous solution containing 1 - 78 mg sertraline HCl/ml:

Sertraline Hydrochloride: 1 - 78 mg

Ethanol: 100 - 500 mg

Glycerin: sufficient quantity to produce 1 ml

- 5 Dissolve the drug substance in a mixture of ethanol and glycerin with stirring.

EXAMPLE 6

1000 ml concentrate solution (20 mg sertraline/ml) with peppermint flavoring:

Sertraline HCl : 22.4 g

Ethanol (95%): 127 g

- 10 Natural Peppermint Stick flavoring: 0.01 - 1.7 g

Glycerin: 852 - 872 g or sufficient quantity to produce 1000 ml

Dissolve the natural peppermint stick flavoring and drug in a mixture of ethanol and glycerin.

EXAMPLE 7

- 15 1000 ml concentrate solution (20 mg sertraline/ml) with menthol flavoring:

Sertraline HCl : 22.4 g

Ethanol (95%): 127 g

Menthol: 0.01 - 1.7 g

Glycerin: 852 - 872 g or sufficient quantity to produce 1000 ml

- 20 Dissolve the menthol and drug in a mixture of ethanol and glycerin.

EXAMPLE 8

1000 ml concentrate solution (20 mg sertraline/ml) with preservatives and peppermint flavoring:

Sertraline HCl : 22.4 g

- 25 Ethanol, anhydrous: 127 g

Natural Peppermint Stick flavoring: 1.7 g

Methylparaben: 0.6 g

Propylparaben: 0.3 g

Glycerin: 852 - 872 g or sufficient quantity to produce 1000 ml

- 30 The natural peppermint stick flavoring, parabens and drug were dissolved in a mixture of ethanol/glycerin.

EXAMPLE 9

1000 ml concentrate solution (20 mg sertraline/ml) with preservatives and no flavoring:

Sertraline HCl : 22.4 g

Ethanol, anhydrous: 127 g

Methylparaben: 0.6 g

Propylparaben: 0.3 g

- 5 Glycerin: 852 - 872 g or sufficient quantity to produce 1000 ml

The parabens and drug were dissolved in a mixture of ethanol/glycerin.

EXAMPLES 10-30

The following examples describe various 1000 ml concentrate solutions of sertraline hydrochloride (20 mg sertraline/ml) with preservatives and menthol flavoring:

10 EXAMPLE 10

Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

Menthol: 0.5 g

Citric acid: 0.1 g

- 15 Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

EXAMPLE 11

Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

Menthol: 0.5 g

- 20 Propyl gallate: 0.1 g

Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

EXAMPLE 12

Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

- 25 Menthol: 0.5 g

BHA: 0.1 g

Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

EXAMPLE 13

Sertraline HCl: 22.7 g

- 30 Ethanol, 95%: 151.0 g

Menthol: 0.5 g

Sodium metabisulfite: 0.5 g

Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

EXAMPLE 14

Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

Menthol: 0.5 g

Ascorbyl palmitate: 0.1 g

- 5 Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

EXAMPLE 15

Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

Menthol: 0.5 g

- 10 Sodium bisulfite: 0.5 g

Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

EXAMPLE 16

Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

- 15 Menthol: 0.5 g

Triethanolamine: 0.1 - 0.5 g

Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

EXAMPLE 17

Sertraline HCl: 22.7 g

- 20 Ethanol, 95%: 151.0 g

Menthol: 0.5 g

BHT: 0.1 g

Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

EXAMPLE 18

- 25 Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

Menthol: 0.5 g

1N sodium hydroxide: 0.03 g

Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

- 30 EXAMPLE 19

Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

Menthol: 0.5 g

Disodium EDTA: 0.1 g

Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

EXAMPLE 20

Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

5 Menthol: 0.5 g

Ascorbic acid: 0.1 g

Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

EXAMPLE 21

Sertraline HCl: 22.7 g

10 Ethanol, 95%: 151.0 g

Menthol: 0.5 g

Thioglycerol: 1.0 g

Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

EXAMPLE 22

15 Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

Menthol: 0.5 g

Sodium thiosulfate: 0.5 g

Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

20 EXAMPLE 23

Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

Menthol: 0.5 g

BHT: 0.1 g

25 BHA: 0.1 g

Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

EXAMPLE 24

Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

30 Menthol: 0.5 g

BHT: 0.1 g

BHA: 0.1 g

Citric acid: 0.1 g

Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

EXAMPLE 25

Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

Menthol: 0.5 g

5 BHT: 0.1 g

BHA: 0.1 g

Propyl gallate: 0.1 g

Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

EXAMPLE 26

10 Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

Menthol: 0.5 g

Disodium EDTA: 0.1 g

Sodium metabisulfite: 0.5 g

15 Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

EXAMPLE 27

Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

Menthol: 0.5 g

20 Cystiene: 1.0 g

Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

EXAMPLE 28

Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

25 Menthol: 0.5 g

BHT: 0.1 g

BHA: 0.1 g

Triethanolamine: 0.1 - 0.5 g

Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

30 EXAMPLE 29

Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

Menthol: 0.5 g

Disodium EDTA: 0.1 g

BHT: 0.1 g

BHA: 0.1 g

Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

EXAMPLE 30

5 Sertraline HCl: 22.7 g

Ethanol, 95%: 151.0 g

Menthol: 0.5 g

Disodium EDTA: 0.1 g

BHA: 0.1 g

10 Glycerin: 1010.7 g or sufficient quantity to produce 1000 ml

For Examples 10-30 above, the menthol and preservative were dissolved in ethanol.

Glycerin was added and dispersed. The drug was added and dissolved.

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CLAIMS

1. A pharmaceutical composition which comprises:
an essentially nonaqueous, liquid concentrate for oral administration
comprising an amount of sertraline or a pharmaceutically acceptable salt thereof and
5 one or more essentially nonaqueous pharmaceutically acceptable excipients; wherein
at least one of the excipients is liquid.
2. The composition of claim 1 which comprises a therapeutically effective amount
of sertraline or a pharmaceutically acceptable salt thereof.
3. The composition of claim 2 wherein the pharmaceutically acceptable salt of
10 sertraline is the hydrochloride salt or the mesylate salt.
4. The composition of claim 1 wherein the excipients are selected from the
group consisting of ethanol, glycerin, polyethylene glycol and propylene glycols.
5. The composition of claim 4 wherein the excipients are ethanol and glycerin.
6. The composition of claim 1 wherein the concentrate comprises sertraline
15 hydrochloride in an amount of about 15 to about 30 mg/ml and wherein the excipients
are ethanol and glycerin in an amount of about 8 to about 20% ethanol (by weight) in
glycerin.
7. The composition of claim 6 wherein the concentrate further comprises one or
more flavoring agents and one or more pharmaceutically acceptable preservatives.
- 20 8. The composition of claim 7 wherein the flavoring agents are selected from the
group consisting of peppermint, spearmint and menthol; and wherein the
preservatives are selected from the group consisting of butylhydroxytoluene,
butylated hydroxyanisole, propyl gallate, ascorbic acid, ascorbyl palmitate, sodium
metabisulfite, sodium bisulfite, sodium thiosulfate, sodium hydroxide, cysteine,
25 ethylenediamine tetraacetic acid or salts thereof, citric acid, triethanolamine,
thioglycerol, methylparaben and propylparaben.
9. The composition of claim 8 wherein the flavoring agent is menthol and
wherein the preservative is butylhydroxytoluene.
10. The composition of claim 9 wherein each ml of the concentrate comprises
30 about 22.4 mg of sertraline hydrochloride, about 151 mg of ethanol, about 0.50 mg of
menthol, about 0.10 mg of butylhydroxytoluene, and about 1011 mg of glycerin.
11. The compound, (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-
naphthalenamine methanesulfonate.

12. A method of using an essentially nonaqueous, liquid concentrate of sertraline or a pharmaceutically acceptable salt thereof to prepare an aqueous solution of sertraline which comprises diluting the concentrate in an aqueous diluent prior to oral administration.
- 5 13. The method of claim 12 wherein the pharmaceutically acceptable salt of sertraline is the hydrochloride salt or the mesylate salt.
14. The method of claim 12 wherein the diluent is selected from the group consisting of water, orange juice, ginger ale, lemon-lime soda and lemonade.
15. A method of treating or preventing diseases or conditions which are caused
10 by disorders of the serotonergic system which comprises:
- a) diluting an essentially nonaqueous, liquid concentrate of setraline or a pharmaceutically acceptable salt thereof in an aqueous diluent; and
- b) orally administering the resulting aqueous solution to a patient in need thereof.
- 15 16. The method of claim 15 wherein the diluent is selected from the group consisting of: water, orange juice, ginger ale, lemon-lime soda and lemonade.
17. A method of treating or preventing diseases or conditions selected from the group consisting of depression, anorexia, chemical dependencies, anxiety-related disorders, premature ejaculation, cancer and post myocardial infarction, which
20 comprises:
- a) diluting an essentially nonaqueous, liquid concentrate of setraline or a pharmaceutically acceptable salt thereof in an aqueous diluent; and
- b) orally administering the resulting aqueous solution to a patient in need thereof.
- 25 18. The method of claim 17 wherein the anxiety-related disorders are selected from the group consisting of: panic disorder, obsessive-compulsive disorder, generalized anxiety disorder, phobias, post traumatic stress disorder and avoidant personality disorder.
19. The method of claim 17 wherein the diluent is selected from the group
30 consisting of: water, orange juice, ginger ale, lemon-lime soda and lemonade.

The present invention provides an essentially nonaqueous, liquid pharmaceutical concentrate composition for oral administration containing sertraline or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients. The present invention also provides a use of this concentrate composition to prepare an aqueous solution of sertraline. In addition, the present invention provides a method of using this concentrate composition to treat or prevent a variety of diseases or conditions. Finally, the present invention provides the compound, (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine methanesulfonate.

10 naphthalenamine methanesulfonate.

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+

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63) <input checked="" type="checkbox"/> Declaration submitted with Initial Filing <input type="checkbox"/> Declaration Submitted after Initial Filing (surcharge 37 CFR 1.16 (e) required)	Attorney Docket Number	PC10139A MAG
	First Named Inventor	Nancy J. Harper
	COMPLETE IF KNOWN	
	Application Number	To be assigned
	Filing Date	Herewith
	Group Art Unit	To be assigned
	Examiner Name	To be assigned

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Sertraline Oral Concentrate

(Title of the Invention)

the specification of which
☒ is attached hereto

OR

☐ was filed on (MM/DD/YYYY) _____ as United States Application Number or PCT International

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I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

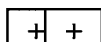
Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached?	
				YES	NO
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below:

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60/104,024	October 13, 1998	

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DECLARATION ---- Utility or Design Patent Application

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U.S. Parent Application Number or PCT
Parent Number

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Parent Patent Number
(if applicable)

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor:

☐ A petition has been filed for this unsigned inventor

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Nancy J.

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Inventor's
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PTO/SB/02A(3/97)

Approved for use through 09/30/98. OMB 0651-0032

DECLARATION	ADDITIONAL INVENTOR(S) Supplemental Sheet
--------------------	--

Name of Additional Joint Inventor, if any:		<input type="checkbox"/> A petition has been filed for this unsigned inventor					
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Willard M.				Welch			
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Name of Additional Joint Inventor, if any:		<input type="checkbox"/> A petition has been filed for this unsigned inventor					
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Inventor's Signature						Date	
Residence: City		State		Country		Citizenship	
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City						Country	

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Inventor's Signature						Date	
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